# Novel Direct Tetrahydropyranylation of Alcohols with Tetrahydropyran and Tetra-n-butylammonium Peroxydisulfate

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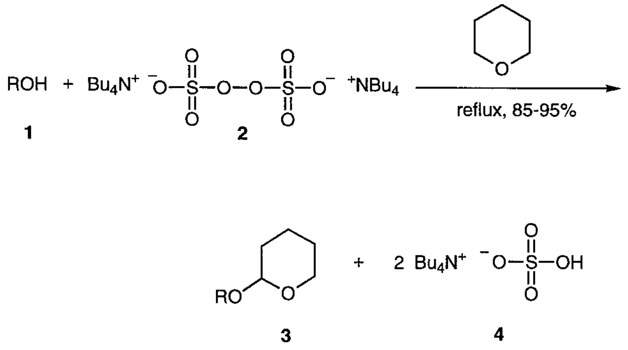
Various alcohols containing functional groups such as olefin, sulfide, and acetal moiety reacted with tetrahydropyran in the presence of tetra-n-butylammonium peroxydisulfate to give 2-tetrahydropyranyl-ethers in excellent yields under nearly neutral condition.

The protection of hydroxyl groups has been extensively investigated and frequently used for the synthesis of polyfunctional compounds.[1,2] In the acetal series, 2-tetrahydropyranyl ethers (THPE) have been practically used[1] and the protecting group can be readily removed with various reagents.[3]

Earlier works on the preparations of THPE, dihydropyran has been used as a starting material with an appropriate acid catalyst: p-toluene-sulfonic acid,[4] pyridinium p-toluene sulfonate[5] and amberlyte H-15.[6] In the course of study on oxidation of alcohols with tetra-n-butylammonium peroxydisulfate **2**[7]. We have found that various alcohols containing functional groups such as olefin, sulfide, and acetal moiety react directly with tetrahydropyran in the presence of **2** to give the corresponding THPE in excellent yields under nearly neutral condition as shown in Scheme 1.

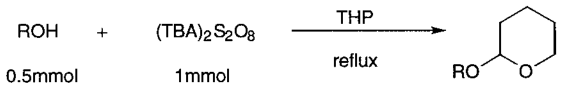


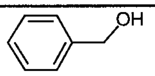
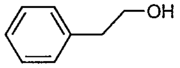
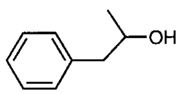
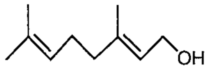
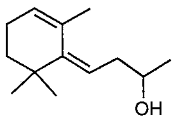
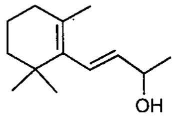
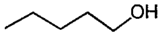
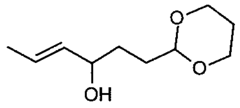
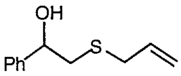
**Scheme 1**

The known inorganic peroxydisulfates of $K_2S_2O_8$ or $Na_2S_2O_8$ are soluble only in water and known to be a strong oxidizing agent in aqueous media. Thermal and photochemical decomposition of $S_2O_8^{2-}$ provides the radical anion $\bullet OSO_3^-$[8-11] which is an effective electron transfer agent.[8] The sulfate radical anion reacts with $H_2O$ to form hydroxyl radical and hydrogen peroxide.[8] It has been demonstrated that the alkoxy radical is generated from a sulfate radical anion and alcohols in aqueous medium by one electron transfer from the alcohols to **2**, and that the alkoxy radical fragments further to the alkyl radicals.[12,13]

In contrast to the metal peroxydisulfates, **2** is very soluble in organic solvents. Thus, the tetrahydropyranylation can be smoothly carried out under anhydrous conditions. The results obtained are summarized in Table 1. In our procedure, fragmentation reactions expected from hydroxyl- or alkyl-radicals were not observed. The alcohols containing olefins converted into **3** without epoxidation of the double bond (run 4,5,6,8 and 9). In the previous reports, sulfides were reported to be oxidized to sulfoxides with potassium peroxydisulfate[14] in aqueous medium and oxidized to sulfones with tetra n-butylammonium monosulfate[15]. However, the secondary benzylic alcohol was tetrahydropyranylated (90%) without oxidation of the sulfide moiety to sulfoxide or sulfone (run 9).

**Table 1.** Protection of alcohols with $(TBA)_2S_2O_8$ in THP



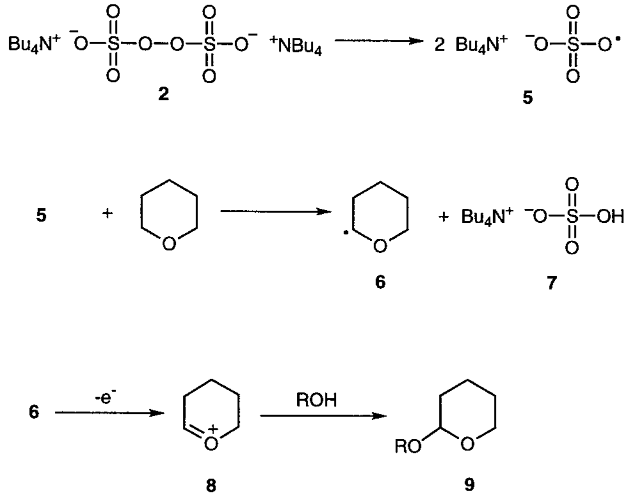
| Run | Substrate | Time | Yield[a] (%) |
|---|---|---|---|
| 1 |  | 3 | 94 |
| 2 |  | 3 | 92 |
| 3 |  | 4 | 95 |
| 4 |  | 6 | 87 |
| 5 |  | 9 | 86 |
| 6 |  | 11 | 85 |
| 7 |  | 4 | 94[b] |
| 8 |  | 8 | 88 |
| 9 |  | 6 | 90 |

a. Isolated yield. b. The yield was determined by GC.

Moreover, alcohols possessing acid-sensitive functional groups such as allylic hydroxy or acetal groups could be smoothly tetrahydropyranylated without destroying these functional groups (run 4,8). Oxidation labile alcohols of benzylic alcohols (run 1,9) and allylic alcohols were converted into their THPE in good yields (run 4,5).

It has been well documented that homolysis of inorganic peroxydisulfate forms the sulfate radical anion intermediate and that it converts into the hydrogen sulfate anion in the oxidation reactions.[8-11] In our experiment tetra-n-butylammonium hydrogen sulfate (**4**) was actually obtained in ca. 80% and confirmed by comparing the melting point with that of the authentic sample. The tetrahydropyranylation of alcohols appears to be inititated by forming tetra-n-butylammonium sulfate radical anion, which abstracts the hydrogen atom at 2-position of higher electron density in THP to form tetrahydropyranyl radical **6**.

One electron oxidation of **6** forms oxonium intermediate **8**. Addition of alcohols to **8** may result in the product **9** as shown in Scheme 2.



**Scheme 2**

In summary, although the mechanism of this new interesting reaction is not yet clear, the reaction may be useful for the practical protection of hydroxy groups.

**Typical Procedure of Tetrahydropyranylation of Alcohols:** The reaction mixture of benzyl alcohol (1 mmol, 108 mg) and tetra-n-butylammonium peroxydisulfate (1.4 mmol, 984 mg) in anhydrous THP (2 ml) was refluxed with stirring. After 3 h, the reaction mixture was concentrated under reduced pressure, filtered, and washed with ether. Water was added to the residue and then extracted with ether (15 ml x 2). The combined ether layer was dried over anhydrous magnesium sulfate, filtered, and then concentrated to give residual oil, which was purified by column chromatography (silica gel, eluent; ether: n-hexane = 1 : 6, v/v) to give the tetrahydropyranyl ether of benzyl alcohol (94%; $^1$H NMR ($CDCl_3$) $\delta$ 1.4-1.8 (m, 6H, $3CH_2$), 3.3-4.1 (m, 2H, $CH_2O$), 4.6 (dd, 2H, $PhCH_2O$), 4.7 (m, 1H, O–CH–O), 7.3 (s, 5H, $C_6H_4$).

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(7) The mixture of potassium peroxydisulfate and two equivalent of tetrabutylammonium hydrogen sulfate in water (240 ml) was stirred for 30 min at 25 °C and then extracted with methylene chloride, dried, filtered, and concentrated to give a white crystalline precipitate which was well washed with pure water, and then dried at 25 °C under vacuum in a desicator for two days. Elemental analysis met tetra-n-butylammonium peroxydisulfate **2**. Oxidation of primary or secondary alcohols with **2** gave the corresponding aldehydes or ketones in benzene, $CH_2Cl_2$ or acetone (unpublished data). But the same reactions in tetrahydropyran resulted in 2-tetrahydropyranyl ethers.

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